REMARKS/ARGUMENTS

Claims 58-65 and 68-70 are pending in this application. Applicants note and appreciate the withdrawal of the earlier objection to the specification and rejection under 35 U.S.C. §112, second paragraph.

The remaining rejections of claims 58-65 and 68-70 under 35 U.S.C. §§101 and 112, first paragraph are addressed below.

35 U.S.C. §§ 101 and 112, First Paragraph

The rejection of claims 58-65 and 68-70 for alleged lack of a credible, specific and substantial asserted utility or a well established utility, and for alleged lack of sufficient teaching for how to use the invention has been maintained from the previous Office Action.

In addressing Applicants' earlier arguments, the Examiner notes that "[n]o evidence has been submitted that it is the norm rather than the exception that protein levels are increased when gene amplification occurs in cancer." Therefore, the Examiner maintained the earlier position that in view of Pennica et al., Konopka et al., and Haynes et al., the skilled artisan would not assume a correlation between gene amplification and protein expression, "but would perform the experiment to verify it." From this the Examiner concludes that "it is not the norm that gene amplification, or even increased transcription, results in increased protein levels."

Applicants disagree, and respectfully traverse the rejection.

First of all, Applicants submit that Haynes et al. does not support the Examiner's position. Haynes et al. teaches that "**there was a general trend** but no strong correlation between protein [expression] and transcript levels" (Emphasis added). Haynes studied 80 *yeast* proteins to show that "protein levels cannot be **accurately** predicted from the level of the corresponding mRNA transcript" (Emphasis added) (see page 1863, paragraph 2.1, last line). For example, in Figure 1, there is a positive correlation between mRNA and protein amongst **most** of the 80 yeast proteins studied but the correlation is "not linear" and hence, "one cannot **accurately** predict protein levels from mRNA levels." In fact, very <u>few</u> data points deviated or scattered away from the expected normal or showed a lack of correlation between mRNA:

protein levels. Thus, contrary to the Examiner's reading, the Haynes data shows that it is more likely than not that a positive correlation exists between mRNA and protein levels.

Secondly, there are additional articles to show that generally, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. For example, Ornoft *et al.* (*Mol. and Cell. Proteomics*, 2002, Vol.1, pages 37-45, copy enclosed) studied transcript levels of 5600 genes in malignant bladder cancers many of which were linked to the gain or loss of chromosomal material using an array-based method. Ornoft *et al.* showed that there was a gene dosage effect and taught that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* (*Cancer Res.*, 2002, Vol. 62, pages 6240-45, copy enclosed) showed, using CGH analysis and cDNA microarrays which compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there was "evidence of a prominent global influence of copy number changes on gene expression levels." (see page 6244, column 1, last paragraph). Additional supportive teachings were also provided by Pollack *et al.*, (*PNAS*, 2002, Vol. 99, pages 12963-12968, copy enclosed) who studied a series of primary human breast tumors and showed that "...62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that in general, gene amplification increases mRNA expression.

Finally, enclosed is a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about

30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis Declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Thus, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO351 gene, that the PRO351 polypeptide is concomitantly overexpressed. Thus, Applicants submit that the PRO351 polypeptides and nucleic acids have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the protein for diagnosis of cancer.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejections.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further

issues outstanding, the Examiner is invited to contact the undersigned at the telephone number provided below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2630P1C10**).

Respectfully submitted,

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DECLARATION OF PAUL POLAKIS, Ph.D.

I, Paul Polakis, Ph.D., declare and say as follows:

1. I was awarded a Ph.D. by the Department of Biochemistry of the Michigan State University in 1984. My scientific Curriculum Vitae is attached to and forms part of this Declaration (Exhibit A).

2. I am currently employed by Genentech, Inc. where my job title is Staff Scientist. Since joining Genentech in 1999, one of my primary responsibilities has been leading Genentech's Tumor Antigen Project, which is a large research project with a primary focus on identifying tumor cell markers that find use as targets for both the diagnosis and treatment of cancer in humans.

3. As part of the Tumor Antigen Project, my laboratory has been analyzing differential expression of various genes in tumor cells relative to normal cells. The purpose of this research is to identify proteins that are abundantly expressed on certain tumor cells and that are either (i) not expressed, or (ii) expressed at lower levels, on corresponding normal cells. We call such differentially expressed proteins "tumor antigen proteins". When such a tumor antigen protein is identified, one can produce an antibody that recognizes and binds to that protein. Such an antibody finds use in the diagnosis of human cancer and may ultimately serve as an effective therapeutic in the treatment of human cancer.

4. In the course of the research conducted by Genentech's Tumor Antigen Project, we have employed a variety of scientific techniques for detecting and studying differential gene expression in human tumor cells relative to normal cells, at genomic DNA, mRNA and protein levels. An important example of one such technique is the well known and widely used technique of microarray analysis which has proven to be extremely useful for the identification of mRNA molecules that are differentially expressed in one tissue or cell type relative to another. In the course of our research using microarray analysis, we have identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, we have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. We have then compared the levels of mRNA and protein in both the tumor and normal cells analyzed.

5. From the mRNA and protein expression analyses described in paragraph 4 above, we have observed that there is a strong correlation between changes in the level of mRNA present in any particular cell type and the level of protein

expressed from that mRNA in that cell type. In approximately 80% of our observations we have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells.

6. Based upon my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. While there have been published reports of genes for which such a correlation does not exist, it is my opinion that such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 5/07/04

By: Paul Polakis

Paul Polakis, Ph.D.

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CURRICULUM VITAE

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1999- 2002	Senior Scientist, Genentech, Inc., S. San Francisco, CA
1997 -1999	Research Director Onyx Pharmaceuticals, Richmond, CA
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1991-1992	Senior Scientist, Chiron Corporation, Emeryville, CA.
1989-1991	Scientist, Cetus Corporation, Emeryville CA.
1987-1989	Postdoctoral Research Associate, Genentech, Inc., South SanFrancisco, CA.
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PUBLICATIONS:

1. **Polakis, P G.** and Wilson, J. E. 1982 Purification of a Highly Bindable Rat Brain Hexokinase by High Performance Liquid Chromatography. **Biochem. Biophys. Res. Commun**. 107, 937-943.

2. **Polakis, P.G**. and Wilson, J. E. 1984 Proteolytic Dissection of Rat Brain Hexokinase: Determination of the Cleavage Pattern during Limited Digestion with Trypsin. **Arch. Biochem. Biophys**. 234, 341-352.

3. **Polakis, P. G**. and Wilson, J. E. 1985 An Intact Hydrophobic N-Terminal Sequence is Required for the Binding Rat Brain Hexokinase to Mitochondria. **Arch. Biochem. Biophys**. 236, 328-337.

4. Uhing, R.J., **Polakis,P.G**. and Snyderman, R. 1987 Isolaton of GTP-binding Proteins from Myeloid HL60 Cells. **J. Biol. Chem**. 262, 15575-15579.

5. **Polakis, P.G**., Uhing, R.J. and Snyderman, R. 1988 The Formylpeptide Chemoattractant Receptor Copurifies with a GTP-binding Protein Containing a Distinct 40 kDa Pertussis Toxin Substrate. **J. Biol. Chem**. 263, 4969-4979.

6. Uhing, R. J., Dillon, S., **Polakis, P. G**., Truett, A. P. and Snyderman, R. 1988 Chemoattractant Receptors and Signal Transduction Processes in Cellular and Molecular Aspects of Inflammation (Poste, G. and Crooke, S. T. eds.) pp 335-379.

7. **Polakis, P.G.**, Evans, T. and Snyderman 1989 Multiple Chromatographic Forms of the Formylpeptide Chemoattractant Receptor and their Relationship to GTP-binding Proteins. **Biochem. Biophys. Res. Commun**. 161, 276-283.

8. **Polakis, P. G.**, Snyderman, R. and Evans, T. 1989 Characterization of G25K, a GTP-binding Protein Containing a Novel Putative Nucleotide Binding Domain. **Biochem. Biophys. Res. Comun.** 160, 25-32.

9. **Polakis, P.**, Weber,R.F., Nevins,B., Didsbury, J. Evans,T. and Snyderman, R. 1989 Identification of the ral and rac1 Gene Products, Low Molecular Mass GTP-binding Proteins from Human Platelets. **J. Biol. Chem**. 264, 16383-16389.

10. Snyderman, R., Perianin, A., Evans, T., **Polakis, P.** and Didsbury, J. 1989 G Proteins and Neutrophil Function. In ADP-Ribosylating Toxins and G Proteins: Insights into Signal Transduction. (J. Moss and M. Vaughn, eds.) Amer. Soc. Microbiol. pp. 295-323.

11. Hart, M.J., **Polakis, P.G.**, Evans, T. and Cerrione, R.A. 1990 The Identification and Charaterization of an Epidermal Growth Factor-Stimulated Phosphorylation of a Specific Low Molecular Mass GTP-binding Protein in a Reconstituted Phospholipid Vesicle System. **J. Biol. Chem**. 265, 5990-6001.

12. Yatani, A., Okabe, K., **Polakis, P.** Halenbeck, R. McCormick, F. and Brown, A. M. 1990 ras p21 and GAP Inhibit Coupling of Muscarinic Receptors to Atrial K^+ Channels. **Cell**. 61, 769-776.

13. Munemitsu, S., Innis, M.A., Clark, R., McCormick, F., Ullrich, A. and **Polakis, P.G.** 1990 Molecular Cloning and Expression of a G25K cDNA, the Human Homolog of the Yeast Cell Cycle Gene CDC42. **Mol. Cell. Biol**. 10, 5977-5982.

14. Polakis, P.G. Rubinfeld, B. Evans, T. and McCormick, F. 1991 Purification of Plasma Membrane-Associated GTPase Activating Protein (GAP) Specific for rap-1/krev-1 from HL60 Cells. **Proc. Natl. Acad. Sci. USA** 88, 239-243.

15. Moran, M. F., **Polakis, P.**, McCormick, F., Pawson, T. and Ellis, C. 1991 Protein Tyrosine Kinases Regulate the Phosphorylation, Protein Interactions, Subcellular Distribution, and Activity of p21ras GTPase Activating Protein. **Mol. Cell. Biol**. 11, 1804-1812

16. Rubinfeld, B., Wong, G., Bekesi, E. Wood, A. McCormick, F. and **Polakis, P. G.** 1991 A Synthetic Peptide Corresponding to a Sequence in the GTPase Activating Protein Inhibits $p21^{ras}$ Stimulation and Promotes Guanine Nucleotide Exchange. **Internatl. J. Peptide and Prot. Res**. 38, 47-53.

17. Rubinfeld, B., Munemitsu, S., Clark, R., Conroy, L., Watt, K., Crosier, W., McCormick, F., and **Polakis, P.** 1991 Molecular Cloning of a GTPase Activating Protein Specific for the Krev-1 Protein $p21^{rap1}$. **Cell** 65, 1033-1042.

18. Zhang, K. Papageorge, A., G., Martin, P., Vass, W. C., Olah, Z., **Polakis, P.**, McCormick, F. and Lowy, D, R. 1991 Heterogenous Amino Acids in RAS and Rap1A Specifying Sensitivity to GAP Proteins. **Science** 254, 1630-1634.

19. Martin, G., Yatani, A., Clark, R., **Polakis, P.**, Brown, A. M. and McCormick, F. 1992 GAP Domains Responsible for $p21^{ras}$-dependent Inhibition of Muscarinic Atrial K^+ Channel Currents. **Science** 255, 192-194.

20. McCormick, F., Martin, G. A., Clark, R., Bollag, G. and **Polakis, P** . 1992 Regulation of p21ras by GTPase Activating Proteins. Cold Spring Harbor **Symposia on Quantitative Biology**. Vol. 56, 237-241.

21. Pronk, G. B., **Polakis, P.**, Wong, G., deVries-Smits, A. M., Bos J. L. and McCormick, F. 1992 $p60^{v\text{-}src}$ Can Associate with and Phosphorylate the $p21^{ras}$ GTPase Activating Protein. **Oncogene** 7,389-394.

22. Polakis P. and McCormick, F. 1992 Interactions Between $p21^{ras}$ Proteins and Their GTPase Activating Proteins. In **Cancer Surveys** (Franks, L. M., ed.) 12, 25-42.

23. Wong, G., Muller, O., Clark, R., Conroy, L., Moran, M., **Polakis,P.** and McCormick, F. 1992 Molecular coloning and nucleic acid binding properties of the GAP-associated tyrosine phosphoprotein p62. **Cell** 69, 551-558.

24. Polakis, P., Rubinfeld, B. and McCormick, F. 1992 Phosphorylation of rap1GAP in vivo and by cAMP-dependent Kinase and the Cell Cycle $p34^{cdc2}$ Kinase in vitro. **J. Biol. Chem.** 267, 10780-10785.

25. McCabe, P.C., Haubrauck, H., **Polakis, P.**, McCormick, F., and Innis, M. A. 1992 Functional Interactions Between $p21^{rap1A}$ and Components of the Budding pathway of *Saccharomyces cerevisiae*. **Mol. Cell. Biol.** 12, 4084-4092.

26. Rubinfeld, B., Crosier, W.J., Albert, I., Conroy,L., Clark, R., McCormick, F. and **Polakis, P.** 1992 Localization of the rap1GAP Catalytic Domain and Sites of Phosphorylation by Mutational Analysis. **Mol. Cell . Biol.** 12, 4634-4642.

27. Ando, S., Kaibuchi, K., Sasaki, K., Hiraoka, T., Nishiyama, T., Mizuno, T., Asada, M., Nunoi, H., Matsuda, I., Matsuura, Y., **Polakis, P.**, McCormick, F. and Takai, Y. 1992 Post-translational processing of rac p21s is important both for their interaction with the GDP/GTP exchange proteins and for their activation of NADPH oxidase. **J. Biol. Chem.** 267, 25709-25713.

28. Janoueix-Lerosey, I., **Polakis, P.**, Tavitian, A. and deGunzberg, J. 1992 Regulation of the GTPase activity of the ras-related rap2 protein. **Biochem. Biophys. Res. Commun.** 189, 455-464.

29. Polakis, P. 1993 GAPs Specific for the rap1/Krev-1 Protein. in GTP-binding Proteins: the *ras*-superfamily. (J.C. LaCale and F. McCormick, eds.) 445-452.

30. Polakis, P. and McCormick, F. 1993 Structural requirements for the interaction of $p21^{ras}$ with GAP, exchange factors, and its bological effector target. **J. Biol Chem.** 268, 9157-9160.

31. Rubinfeld, B., Souza, B. Albert, I., Muller, O., Chamberlain, S., Masiarz, F., Munemitsu, S. and **Polakis, P.** 1993 Association of the APC gene product with beta- catenin. **Science** 262, 1731-1734.

32. Weiss, J., Rubinfeld, B., **Polakis, P.**, McCormick, F. Cavenee, W. A. and Arden, K. 1993 The gene for human rap1-GTPase activating protein (rap1GAP) maps to chromosome 1p35-1p36.1. **Cytogenet. Cell Genet.** 66, 18-21.

33. Sato, K. Y., **Polakis, P.**, Haubruck, H., Fasching, C. L., McCormick, F. and Stanbridge, E. J. 1994 Analysis of the tumor suppressor acitvity of the K-rev gene in human tumor cell lines. **Cancer Res.** 54, 552-559.

34. Janoueix-Lerosey, I., Fontenay, M., Tobelem, G., Tavitian, A., **Polakis, P.** and DeGunzburg, J. 1994 Phosphorylation of rap1GAP during the cell cycle. **Biochem. Biophys. Res. Commun.** 202, 967-975

35. Munemitsu, S., Souza, B., Mueller, O., Albert, I., Rubinfeld, B., and **Polakis, P.** 1994 The APC gene product associates with microtubules in vivo and affects their assembly in vitro. **Cancer Res.** 54, 3676-3681.

36. Rubinfeld, B. and **Polakis, P.** 1995 Purification of baculovirus produced rap1GAP. **Methods Enz.** 255,31

37. Polakis, P. 1995 Mutations in the APC gene and their implications for protein structure and function. **Current Opinions in Genetics and Development** 5, 66-71

38. Rubinfeld, B., Souza, B., Albert, I., Munemitsu, S. and **Polakis P.** 1995 The APC protein and E-cadherin form similar but independent complexes with α-catenin, β-catenin and Plakoglobin. **J. Biol. Chem.** 270, 5549-5555

39. Munemitsu, S., Albert, I., Souza, B., Rubinfeld, B., and **Polakis, P.** 1995 Regulation of intracellular β-catenin levels by the APC tumor suppressor gene. **Proc. Natl. Acad. Sci.** 92, 3046-3050.

40. Lock, P., Fumagalli, S., **Polakis, P.** McCormick, F. and Courtneidge, S. A. 1996 The human p62 cDNA encodes Sam68 and not the rasGAP-associated p62 protein. **Cell** 84, 23-24.

41. Papkoff, J., Rubinfeld, B., Schryver, B. and **Polakis, P.** 1996 Wnt-1 regulates free pools of catenins and stabilizes APC-catenin complexes. **Mol. Cell. Biol.** 16, 2128-2134.

42. Rubinfeld, B., Albert, I., Porfiri, E., Fiol, C., Munemitsu, S. and **Polakis, P.** 1996 Binding of GSK3β to the APC-β-catenin complex and regulation of complex assembly. **Science** 272, 1023-1026.

43. Munemitsu, S., Albert, I., Rubinfeld, B. and **Polakis, P.** 1996 Deletion of amino-terminal structure stabilizes β-catenin in vivo and promotes the hyperphosphorylation of the APC tumor suppressor protein. **Mol. Cell. Biol.**16, 4088-4094.

44. Hart, M. J., Callow, M. G., Sousa, B. and **Polakis P.** 1996 IQGAP1, a calmodulin binding protein witha rasGAP related domain, is a potential effector for cdc42Hs. **EMBO J.** 15, 2997-3005.

45. Nathke, I. S., Adams, C. L., **Polakis, P.**, Sellin, J. and Nelson, W. J. 1996 The adenomatous polyposis coli (APC) tumor suppressor protein is localized to plasma membrane sites involved in active epithelial cell migration. **J. Cell. Biol.** 134, 165-180.

46. Hart, M. J., Sharma, S., elMasry, N., Qui, R-G., McCabe, P., **Polakis, P.** and Bollag, G. 1996 Identification of a novel guanine nucleotide exchange factor for the rho GTPase. **J. Biol. Chem.** 271, 25452.

47. Thomas JE, Smith M, Rubinfeld B, Gutowski M, Beckmann RP, and **Polakis P.** 1996 Subcellular localization and analysis of apparent 180-kDa and 220-kDa proteins of the breast cancer susceptibility gene, BRCA1. **J. Biol. Chem.** 1996 271, 28630-28635

48. Hayashi, S., Rubinfeld, B., Souza, B., **Polakis, P.**, Wieschaus, E., and Levine, A. 1997 A Drosophila homolog of the tumor suppressor adenomatous polyposis coli

down-regulates β -catenin but its zygotic expression is not essential for the regulation of armadillo. **Proc. Natl. Acad. Sci.** 94, 242-247.

49. Vleminckx, K., Rubinfeld, B., **Polakis, P.** and Gumbiner, B. 1997 The APC tumor suppressor protein induces a new axis in Xenopus embryos. **J. Cell. Biol.** 136, 411-420.

50. Rubinfeld, B., Robbins, P., El-Gamil, M., Albert, I., Porfiri, P. and **Polakis, P.** 1997 Stabilization of β-catenin by genetic defects in melanoma cell lines. **Science** 275, 1790-1792.

51. Polakis, P. The adenomatous polyposis coli (APC) tumor suppressor. 1997 **Biochem. Biophys. Acta**, 1332, F127-F147.

52. Rubinfeld, B., Albert, I., Porfiri, E., Munemitsu, S., and **Polakis, P** 1997 Loss of β-catenin regulation by the APC tumor suppressor protein correlates with loss of structure due to common somatic mutations of the gene. **Cancer Res.** 57, 4624-4630.

53. Porfiri, E., Rubinfeld, B., Albert, I., Hovanes. K., Waterman, M., and **Polakis, P.** 1997 Induction of a β-catenin-LEF-1 complex by wnt-1 and transforming mutants of β-catenin. **Oncogene** 15, 2833-2839.

54. Thomas JE, Smith M, Tonkinson JL, Rubinfeld B, and **Polakis P.,** 1997 Induction of phosphorylation on BRCA1 during the cell cycle and after DNA damage. **Cell Growth Differ.** 8, 801-809.

55. Hart, M., de los Santos, R., Albert, I., Rubinfeld, B., and **Polakis P.**, 1998 Down regulation of β-catenin by human Axin and its association with the adenomatous polyposis coli (APC) tumor suppressor, β-catenin and glycogen synthase kinase 3β. **Current Biology 8,** 573-581.

56. Polakis, P. 1998 The oncogenic activation of β-catenin. **Current Opinions in Genetics and Development** 9, 15-21

57. Matt Hart, Jean-Paul Concordet, Irina Lassot, Iris Albert, Rico del los Santos, Herve Durand, Christine Perret, Bonnee Rubinfled, Florence Margottin, Richard Benarous and **Paul Polakis**. 1999 The F-box protein β–TrCP associates with phosphorylated β–catenin and regulates its activity in the cell. **Current Biology** 9, 207-10.

58. Howard C. Crawford, Barbara M. Fingleton, Bonnee Rubinfeld, **Paul Polakis** and Lynn M. Matrisian 1999 The metalloproteinase matrilysin is a target of β–catenin transactivation in intestinal tumours. **Oncogene** 18, 2883-91.

59. Meng J, Glick JL, **Polakis P**, Casey PJ. 1999 Functional interaction between Galpha(z) and Rap1GAP suggests a novel form of cellular cross-talk. **J Biol Chem.** 17, 36663-9

60. Vijayasurian Easwaran, Virginia Song, **Paul Polakis** and Steve Byers 1999 The ubiquitin-proteosome pathway and serine kinase activity modulate APC mediated regulation of β-catenin-LEF signaling. **J. Biol. Chem**. 274(23):16641-5.

61 **Polakis P**, Hart M and Rubinfeld B. 1999 Defects in the regulation of beta-catenin
in colorectal cancer. **Adv Exp Med Biol**. 470, 23-32

62 Shen Z, Batzer A, Koehler JA, **Polakis P**, Schlessinger J, Lydon NB, Moran MF. 1999 Evidence for SH3 domain directed binding and phosphorylation of Sam68 by Src. **Oncogene**. 18, 4647-53

64. Thomas GM, Frame S, Goedert M, Nathke I, **Polakis P**, Cohen P. 1999 A GSK3- binding peptide from FRAT1 selectively inhibits the GSK3-catalysed phosphorylation of axin and beta-catenin. **FEBS Lett**. 458, 247-51.

65. Peifer M, **Polakis P**. 2000 Wnt signaling in oncogenesis and embryogenesis--a look outside the nucleus. **Science** 287,1606-9.

66. **Polakis P.** 2000 Wnt signaling and cancer. **Genes Dev**;14, 1837-1851.

67. Spink KE, **Polakis P**, Weis WI 2000 Structural basis of the Axin-adenomatous polyposis coli interaction. **EMBO J** 19, 2270-2279.

68. Szeto , W., Jiang, W., Tice, D.A., Rubinfeld, B., Hollingshead, P.G., Fong, S.E., Dugger, D.L., Pham, T., Yansura, D.E., Wong, T.A., Grimaldi, J.C., Corpuz, R.T., Singh J.S., Frantz, G.D., Devaux, B., Crowley, C.W., Schwall, R.H., Eberhard, D.A.,
Rastelli, L., **Polakis, P**. and Pennica, D. 2001 Overexpression of the Retinoic Acid-
Responsive Gene Stra6 in Human Cancers and its Synergistic Induction by Wnt-1 and
Retinoic Acid. **Cancer Res** 61, 4197-4204.

69. Rubinfeld B, Tice DA, **Polakis P**. 2001 Axin dependent phosphorylation of the adenomatous polyposis coli protein mediated by casein kinase 1 epsilon. **J Biol Chem**
276, 39037-39045.

70. **Polakis P**. 2001 More than one way to skin a catenin. **Cell** 2001 105, 563-566.

71. Tice DA, Soloviev I, **Polakis P**. 2002 Activation of the Wnt Pathway Interferes withSerum Response Element-driven Transcription of Immediate Early Genes. **J Biol.**
Chem. 277, 6118-6123.

72. Tice DA, Szeto W, Soloviev I, Rubinfeld B, Fong SE, Dugger DL, Winer J,

Williams PM, Wieand D, Smith V, Schwall RH, Pennnica D, **Polakis P**. 2002 Synergistic activation of tumor antigens by wnt-1 signaling and retinoic acid revealed by gene expression profiling. **J Biol Chem**. 277,14329-14335.

73. **Polakis, P**. 2002 Casein kinase I: A wnt'er of disconnect. **Curr. Biol**. 12, R499.

74. Mao,W. , Luis, E., Ross, S., Silva, J., Tan, C., Crowley, C., Chui, C., Franz, G., Senter, P., Koeppen, H., **Polakis, P.** 2004 EphB2 as a therapeutic antibody drug target for the treatment of colorectal cancer. **Cancer Res**. 64, 781-788.

75. Shibamoto, S., Winer, J., Williams, M., Polakis, P. 2003 A Blockade in Wnt signaling is activated following the differentiation of F9 teratocarcinoma cells. **Exp. Cell Res.** 29211-20.

76. Zhang Y, Eberhard DA, Frantz GD, Dowd P, Wu TD, Zhou Y, Watanabe C, Luoh SM, **Polakis P**, Hillan KJ, Wood WI, Zhang Z. 2004 GEPIS--quantitative gene expression profiling in normal and cancer tissues. **Bioinformatics**, April 8